Amendment To The Drawings:

The attached sheets of drawings include changes to figures 11 and 12 of the drawings as originally filed. These sheets replace the original sheets of figures 11 and 12 of the drawings, respectively.

Attachment: 2 Replacement Sheets, and
2 Annotated Sheets Showing Changes.

REMARKS/ARGUMENTS

Claims 1-58 were pending; claims 9-12, 46-48 and 50-58 were withdrawn from further consideration as directed to non-elected subject matters in the present application before the amendment as set forth above. By this Amendment, claims 5, 6 and 44 are amended, claims 3, 4, 8, 19-43 and 49 are withdrawn. Applicants assert that no new matter is added.

Applicants appreciate the Examiner's careful review of the application.

Restriction Requirements

Applicants respectfully traverse the Examiner's subdividing of the sequence inventions SEQ ID NOs: 1-4 into four separate sub-groups at least for the reasons stated as follows:

(1) The SEQ ID NO: 1-4 are all thrombin variants of wild-type thrombin, with only one or two amino acids variations from the wild-type thrombin.

In addition, these four sequences share the same or corresponding active domains located in the B-chain (i.e., SEQ ID NO: 2 or 4).

They share the same or corresponding specific technical features and therefore are technically related. Thus, SEQ ID NOs: 1-4 belong to one single general inventive concept.

(2) SEQ ID NO: 1 is the sequence of W215A with A-chain and B-chain, and SEQ ID NO: 2 is B-chain only, which is part of SEQ ID NO:1. Thus, SEQ ID NOs: 1 and 2 should belong to the same group.

(3) SEQ ID NO: 3 is the sequence of WE with A-chain and B-chain, and SEQ ID NO: 4 is WE's B-chain only, i.e., part of SEQ ID NO:3. Thus, SEQ ID NOs: 3 and 4 should belong to the same group.

For the forgoing reasons, SEQ ID NOs: 3 and 4 should at least be grouped together. The same reason applies to SEQ ID NOs: 1 and 2. The B-chain is an essential structure for thrombin's activity, and is di-sulfide bond linked to the A-chain. It would not be sensible to carve out the B-chain (i.e., SEQ ID NO: 2 or 4) from the entire protein sequence (i.e., SEQ ID NO: 1 or 3).

Further, since both A- and B-chains sequences of W215A/E217A (i.e., SEQ ID NO: 3 for A- and B- chains, SEQ ID NO: 4 for B-chain) have to be searched, the search for A- and B-chains sequences of W215A would not impose an undue burden to the Examiner. The two

thrombin variants W215A/E217A and W215A have only one amino acid difference in their B-chain structure .

For the foregoing reasons, it is only sensible and fair to the Applicants that SEQ ID NOs: 1-4 be grouped together. Thus, Applicants respectfully request the Examiner re-group the amino acid sequences by combining SEQ ID NOs: 1-4 into one sub-group. Under this circumstance, claims 1, 2, 5-7, 13-18 and 44-45 ought to be examined on their merits.

At the minimum, the SEQ ID NO: 2 should be in the same group as the SEQ ID NO: 1, and the SEQ ID NO: 4 should be in same group as the elected SEQ ID NO: 3. Under this circumstance, claims 1, 2, 5-7, 16-18 and 44-45 ought to be examined on their merits.

Abstract

In the February 21, 2006 Office Action, the Abstract was objected to for "polypeptidess" one line 4.

In response, Applicants have amended the Abstract accordingly to overcome the objection.

Specification Objections

In the February 21, 2006 Office Action, the specification was objected to for (1) not claming priority to the parent application, (2) containing hyperlinks, (3) having blank spaces on page 27 and page 38, and (4) having a large blank space on page 56.

In response, Applicants have amended the specification accordingly to overcome the objections.

Drawings Objections

Figs. 1, 3 and 5

In the February 21, 2006 Office Action, Figs. 1, 3 and 5 were objected as the sequences shown therein appear to be shorter than SEQ ID NO: 1 (295 amino acids), SEQ ID NO: 3 (295 amino acids) and SEQ ID NO: 5 (888 nucleotides), respectively.

Applicants respectfully submit that both Figs. 1 and 3 have an amino acid sequence of exactly 295 residues long, and Fig. 3 has exactly 888 nucleotides.

Both Fig. 1 and Fig. 2 show a sequence that has (1) amino acids numbered 1a~36a for A-chain, and (2) amino acids numbered 1~259 for B-chain. Thus, the sequence in Fig. 1 and Fig. 2 is exactly 295 amino acids long in total.

Fig. 5 shows 888 nucleotides in total (there are 14 rows, 60 nucleotides per row, plus 48 nucleotides in the last row).

Accordingly, Applicants respectfully request that the objections to Figs. 1, 3 and 5 be withdrawn.

Figs. 11c and 12

Figs. 11c and 12 were objected for labeling two different data curves with the same filled circles. Applicants have submitted replacement drawing sheets as attached herein to correct typographical errors. The support for the amendments can be found in the written descriptions as originally filed.

Claim Objections

Claims 5 and 6

The Office Action objected claims 5 and 6 for "ration."

In response, Applicants have amended claims 5 and 6 according to the Examiner's suggestion to overcome the objections.

Clams 44 and 45

The Office Action objected claims 44 and 45 for reciting non-elected subject matter.

Applicants respectfully traverse the objections for the reasons stated above under the heading "Restriction Requirements." Briefly, the SEQ ID NO: 4 (i.e., B-chain) is an essential structure of the SEQ ID NO: 3 (i.e., A-chain plus B-chain). The SEQ ID NO: 4 therefore belongs to the same group as the elected SEQ ID NO: 3. Thus, the SEQ ID NOs: 3 and 4 should have been considered together by the Examiner.

Claim Rejections Under Double Patenting

In the February 21, 2006 Office Action, claims 1, 5-7, 16, 17, 44 and 45 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 5-7, 9, 10, 12 and 13 of the U.S. Patent 6,706,512.

In response, because the scope and/or allowabilities of claims 1, 5-7, 16, 17, 44 and 45 are still pending in relation to 35 U.S.C. § 103, Applicants hereby respectfully submit that a terminal disclaimer, if still required then, would be submitted after all other rejections with respect to these claims have been finally disposed of in a future Office Action.

Claim Rejections – 35 USC § 112 Second Paragraph

In the February 21, 2006 Office Action, claims 44 and 45 were rejected under 35 U. S. C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Office Action states that the term "reduced" is not defined in the claim 44, and claim 45 depends from claim 44.

In response, applicant has amended claim 44 accordingly to provide a relative standard for "reduced" to overcome the rejections.

Claim Rejections – 35 USC § 112 First Paragraph

Enablement:

Claims 1, 5-7, and 16 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. Specifically, the Office Action asserts that the specification, while being enabling for the thrombin variant of SEQ ID NO:3, does not reasonably provide enablement for a thrombin variant that has substitutions W215 and E217 and is at least 80% identical to SEQ ID NO:3.

Applicants respectfully traverse the general enablement rejections made in the Office Action.

The claims meet the enablement requirements since one of ordinary skilled in the art could practice the invention without undue experimentation for the reasons stated as follows:

(1) Nature of the invention:

The invention is directed to a WE variant of a wild-type thrombin. Thrombin has been well characterized in terms of its amino acid sequence, functional domains and properties.

(2) Breadth of claims:

These claims are not unduly broad. Using independent claim 1 as an example, it requires limitations (i) having two substitutions W215A and E217A; and (ii) having the amino acid sequence of at least 80% identical to SEQ ID NO: 3.

(3) Guidance:

The specification provides sufficient guidance to making, testing and using thrombin variants.

(4) Working Examples:

The specification provides working examples for thrombin variants and results of functionality tests

(5) Quantity of experimentation necessary

It would not take undue experimentation for one of skilled in the art in view of the disclosure to quickly narrow down the list of thrombin variants of the claimed invention.

(6) Relative skill of those in the art

To make a protein variant with at least 80% of homology to a known sequence SEQ ID NO:3, and then examine its antithrombotic functionality is within one of the skilled in the art. Thus, there is a reasonable expectation of success for those skilled in the art to make and use the claimed invention.

Written Description:

Claims 1, 7, and 16 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way s to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, has possession of the claimed invention. Specifically, the Office Actions asserts that the specification does not contain any disclosure of the function of all said polypeptides.

Applicants respectfully traverse the general enablement rejections made in the Office Action. These claims are directed to the thrombin variants of WE with at least 80% of amino acid sequence homology. The working examples disclosed in the specification are representative to the function of the claimed thrombin variants. Further, the specification has detail descriptions

of making and testing WE thrombin variants. Thus, Applicants had contemplated and possessed the claimed invention at the time when the application was filed.

Accordingly, Applicants respectfully request that the 35 U.S.C. § 112 first paragraph rejections be withdrawn.

35 U.S.C. §103 Rejections

Claims 1, 5-7, 16, 17, 44 and 45 were rejected under 35 U.S.C. §103(a) as being unpatentable over Gibbs et al., 1995 (IDS) in view of Arosio et al., 2000 (IDS) or Ayala et al., 2001 (meeting date Aug. 23-26, 2000).

Applicants respectfully traverse the rejections at least for the following reasons:

The claimed invention is directed to a thrombin variant having two substitutions W215A and E217A.

Gibbs et al. teaches a single substitution E217A (designated as E229A)of thrombin. Gibbs fails to teach two substitutions, let alone two substitutions W215A and E217A of thrombin.

Arosio et al. also teaches a single substitution of thrombin W215. Arosio fails to teach two substitutions as well, let alone two substitutions W215A and E217A.

Neither Gibbs nor Arosio provides any suggestion or motivation for making a thrombin variant that has two substitutions, let alone two substitutions W215A and E217A.

The Office Action asserts that suggestion to make a thrombin variant comprising both substitutions W215A and E217A was provided by Arosio et al.

On the contrary, Arosio et al. expressly states that "[T]he . . . effect on . . . fibrinogen and protein C makes the W215A mutant the best anticoagulant thrombin reported to date. The gain in anticoagulant potency is larger than that of the E217K mutant." *See* page 8098, right column, first paragraph, lines 9-13.

Since Arosio et al. teaches that a single substitution W215A is the best and has a larger gain in anticoagulant potency than that of E217, skilled artisan in viewing Arosio's teaching at the time when the invention was filed would not have motivation to combine E217 and W215A.

Furthermore, the claimed invention is non-obvious because of the unexpected properties.

The Office Action asserts that suggestion and motivation to combine is based on skilled artisan's desire to provide a thrombin variant with enhanced protein C activity and decreased fibrinogen cleavage.

On the contrary, the combination of E217 and W215A produces a dramatically decreased, rather than enhanced, protein C activity. *See* Table 2 data for Protein C + TM (E217A:W215A:WE = 140:75:33).

The invention has provided a combination product WE that has an synergy effect on reducing the release of fibrinopeptides A and B. See Tables 1 and 2 (Fibrinogen: E217A: W215A:WE = 0.27:0.034:0.00089; Fibrin: E217A: W215A:WE = 0.15:0.053:0.0021)

Therefore, claims 1, 5-7, 16, 17, 44 and 45 are non-obvious over Gibbs et al. in view of Arosio or Ayala et al.

CONCLUSION

Applicant respectfully submits that the foregoing Amendment and Response place this application in condition for allowance. If the Examiner believes that there are any issues that can be resolved by a telephone conference, or that there are any informalities that can be corrected by an Examiner's amendment, please call the undersigned at 404-495-3678.

Respectfully submitted,
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June 20, 2006

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Inventor: Andrus Gruber
Docket No.: 14507-47022
Serial No.: 10/699,393 Filing Date: 10/31/2003
Title: *Anti-Thrombotic Thrombin Variants*
Attorney Name: Tim Tingkang Xia
Phone No.: 404-493-3678
ANNOTATED SHEET

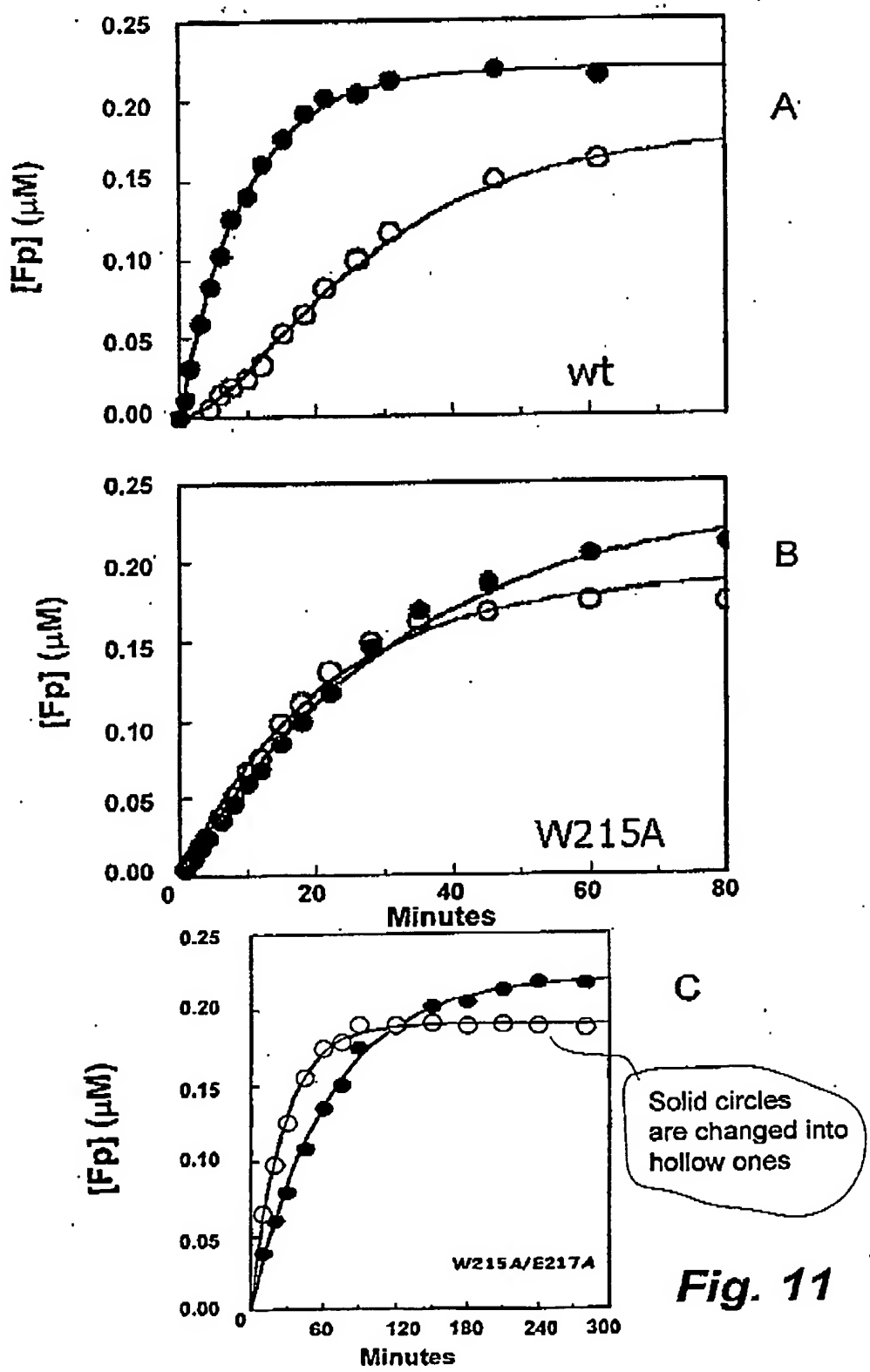

Fig. 11

Inventor: Andras Gruber
Docket No.: 14507-47022
Serial No.: 10/699,393 Filing Date: 10/31/2003
Title: ***Anti-Thrombotic Thrombin Variants***
Attorney Name: Tim Tingkang Xia
Phone No.: 404-493-3678
ANNOTATED SHEET

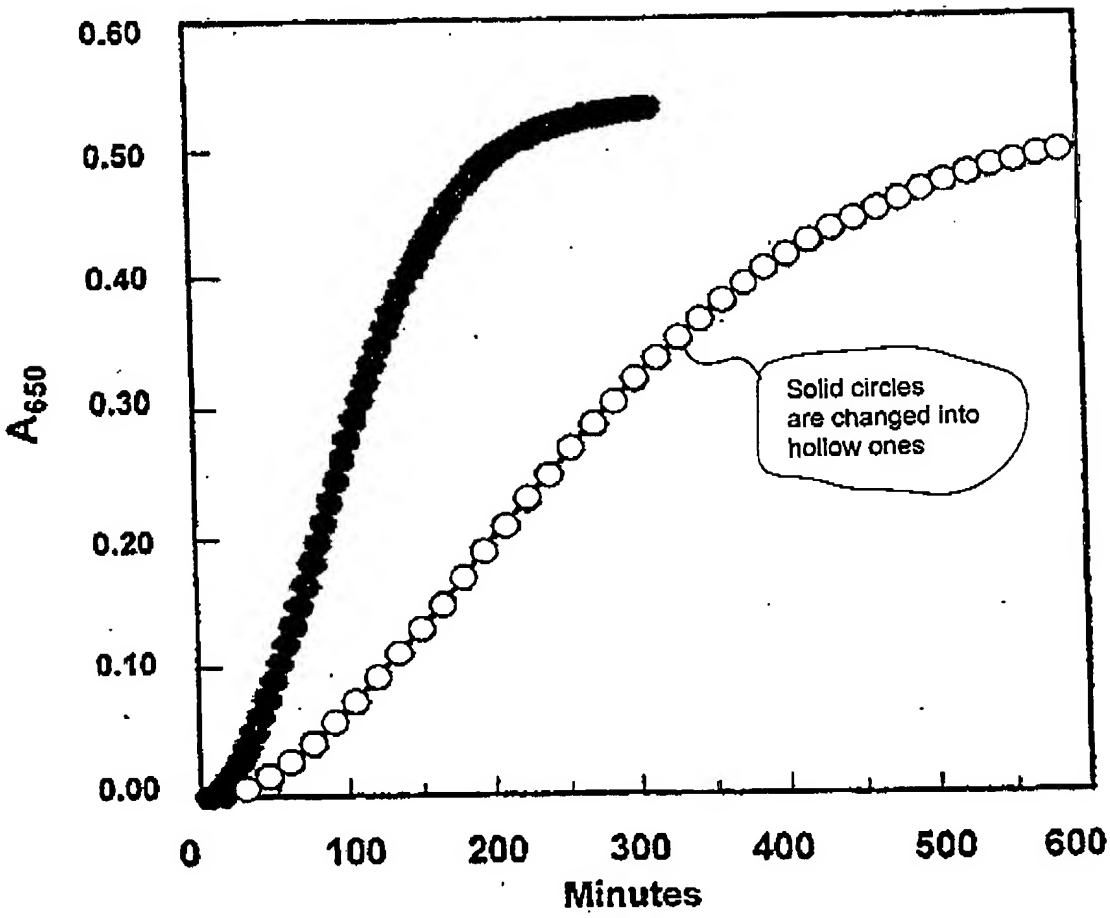

Fig. 12